Application No. 10/766,948 Docket No.: 5999-0524PUS3 Amendment dated June 29, 2007

Reply to Office Action of March 29, 2007

## AMENDMENTS TO THE CLAIMS

# 1. (Currently Amended) A compound having the formula I

$$(R^3)_n$$
  $Q$   $N_1$   $N_1$   $N_2$   $P$   $(R^1)_m$   $(I)$ 

wherein:

X1 is O or S:

X2 is a bond or C1.3alkylene;

P is C3-7cycloalkyl or C4-7cycloalkenyl;

 $R^1 \ \text{is hydrogen,} \ C_{1\text{-}6} alkyl, \ \text{cyano, halogen and} \ C_{1\text{-}6} alkylhalo, \ \text{and one or more} \ R^1 \ \text{may be}$  connected to each other or to one of the atoms that constitutes P to form a bridge or spirocyclo;

 $R^2$  is hydrogen,  $C_{1\cdot 3} alkyl,$  fluoromethyl, difluoromethyl, trifluoromethyl, methoxy,

fluoromethoxy, difluoromethoxy, trifluoromethoxy,  $C_{0-3}$ alkylamino,

C+3alkoxy, hydroxy C0-3alkylhydroxy or C0-3alkyldimethylamino;

 $R^4$  is hydrogen,  $C_{1-3}$  alkyl, fluoromethyl, difluoromethyl, trifluoromethyl, methoxy,

fluoromethoxy, difluoromethoxy, trifluoromethoxy,  $C_{1-3}$ alkylamino,

C1-3alkoxy, hydroxy C0-3alkylhydroxy or C0-3alkyldimethylamino;

Q is a saturated or partially unsaturated ring containing 4, 5, 6 or 7 atoms independently selected from C, S, O and N, and said ring may further contain groups independently selected from SO,

SO2, CO, cyano and CS;

R3 is hydrogen, hydroxy, halogen, nitro, cyano, OC1-3alkylhalo, C1-3alkylhalo, C1-3alkyl,

 $C_{1-3}$ alkoxy $C_{0-3}$ alkyl,  $C_{0-3}$ alkylOhydroxy $C_{2-4}$ alkyl,  $C_{0-3}$ alkylO $C_{2-4}$ hydroxyalkyl,

 $\frac{hydroxyC_{t-3}allkyl,\ C_{l\cdot3}hydroxyalkyl,\ amino,\ C_{l\cdot3}alkylaminoC_{0\cdot3}alkyl,\ (C_{l\cdot3}alkyl)_2aminoC_{0\cdot3}alkyl,\ amide$ 

 $C_{1\text{--}3}alkylamideC_{0\text{--}3}alkyl \ or \ (C_{1\text{--}3}alkyl)_2amideC_{0\text{--}3}alkyl;$ 

n is 0, 1, 2, 3 or 4; and

m is 0, 1, 2, 3 or 4;

or N1-oxides, or salts thereof.

## 2. (Currently Amended) A compound having the formula I

$$(R^3)_n$$
  $Q$   $N_1$   $N_1$   $N_2$   $N_3$   $N_4$   $N_2$   $P$   $(R^1)_n$   $(D)$ 

wherein:

X1 is O or S:

X2 is a bond or C1-3alkylene:

P is C3-7cycloalkyl or C4-7cycloalkenyl;

 $R^1$  is hydrogen,  $C_{1-6}$ alkyl, cyano, halogen and  $C_{1-6}$ alkylhalo, and one or more  $R^1$  may be connected to each other or to one of the atoms that constitutes P to form a bridge or spirocyclo;  $R^2$  is hydrogen,  $C_{1-3}$ alkyl, fluoromethyl, difluoromethyl, trifluoromethyl, methoxy, fluoromethoxy, difluoromethoxy or trifluoromethoxy.

R4 is hydrogen:

Q is a saturated or partially saturated unsaturated ring containing 4, 5, 6 or 7 atoms independently selected from C, S, O and N, and said ring may further contain groups independently selected from SO, SO<sub>2</sub>, CO, cyano and CS;

R<sup>3</sup> is hydrogen, hydroxy, halogen, nitro, OC<sub>1-3</sub>alkylhalo, C<sub>1-3</sub>alkylhalo, C<sub>1-3</sub>alkyl,

 $C_{1-3}$ alkoxy $C_{0-3}$ alkyl, hydroxy $C_{1-3}$ alkyl,  $C_{1-3}$ hydroxyalkyl cyano, amino or amide;

n is 0, 1, 2, 3 or 4; and

m is 0, 1, 2, 3 or 4;

or N1-oxides, or salts thereof.

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- 3. (Original) The compound according to any one of claims 1 or 2, wherein P is  $C_{3-7}$ cycloalkyl substituted with one or more  $R^1$ , wherein  $R^1$  is hydrogen,  $C_{1-6}$ alkyl, cyano, halogen or  $C_{1-6}$ alkylhalo, and one or more  $R^1$  may be connected to each other or to one of the atoms that constitutes P to form a bridge or spirocyclo.
- (Original) The compound according to claim 3, wherein P is C<sub>5.7</sub>cycloalkyl substituted with one or more R<sup>1</sup>, wherein R<sup>1</sup> is methyl.
- (Previously Presented) The compound according to any one of claims 1 or 2, wherein X<sup>1</sup> is oxygen.
- 6. (Previously Presented) The compound according to any one of claims 1 or 2, wherein  $X^2$  is a bond.
- (Previously Presented) The compound according to any one of claims 1 or 2, wherein R<sup>2</sup> is hydrogen.
- 8. (Previously Presented) The compound according to any one of claims 1 or 2, wherein  $\mathbb{R}^4$  is hydrogen or methyl.
- 9. (Previously Presented) The compound according to any one of claims 1 or 2, wherein Q is a saturated or partially unsaturated ring containing 5, 6 or 7 atoms independently selected from C, O and N.
- 10. (Previously Presented) The compound according to any one of claims 1 or 2, wherein R<sup>3</sup> is hydrogen, hydroxy, halogen, cyano, C<sub>1-3</sub>alkyl or C<sub>1-3</sub>alkoxyC<sub>0-3</sub>alkyl.

11. (Previously Presented) The compound according to any one of claims 1 or 2 having a transrelationship between R<sup>1</sup> and X<sup>2</sup> on ring P, wherein P is cyclohexane, and R<sup>1</sup> and X<sup>2</sup> are attached to P at positions 4 and 1, respectively.

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# (Previously Presented) The compounds N-(trans-4-methylcyclohexyl)-5,6,7,8-tetrahydroquinoxaline-2-carboxamide, N-(4,4-dimethylcyclohexyl)-5,6,7,8-tetrahydroquinoxaline-2-carboxamide, or salts thereof.

## 13. (Previously Presented) The compounds

N-(4,4-dimethylcyclohexyl)-3-methyl-5,6,7,8-tetrahydroquinoxaline-2-carboxamide,
8-methyl-N-(trans-4-methylcyclohexyl)-5,6,7,8-tetrahydroquinoxaline-2-carboxamide,
7-hydroxy-5,7-dimethyl-N-(trans-4-methylcyclohexyl)-6,7-dihydro-5H-cyclopenta[b]pyrazine-2-carboxamide.

N-(trans-4-methylcyclohexyl)-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyrazine-2-carboxamide,
7-methyl-N-(trans-4-methylcyclohexyl)-5,6,7,8-tetrahydroquinoxaline-2-carboxamide,
6-methyl-N-(trans-4-methylcyclohexyl)-5,6,7,8-tetrahydroquinoxaline-2-carboxamide,
N-(trans-4-methylcyclohexyl)-6,7-dihydro-5H-cyclopenta[b]pyrazine-2-carboxamide,
N-(trans-4-methylcyclohexyl)-7,8-dihydro-5H-pyrano[3,4-b]pyrazine-2-carboxamide,
N-(trans-4-methylcyclohexyl)-7,8-dihydro-5H-pyrano[3,4-b]pyrazine-3-carboxamide,
7-hydroxy-N-(trans-4-methylcyclohexyl)-5,6,7,8-tetrahydroquinoxaline-2-carboxamide,
6-hydroxy-N-(trans-4-methylcyclohexyl)-5,6,7,8-tetrahydroquinoxaline-2-carboxamide,
N-(4,4-dimethylcyclohexyl)-5,6,7,8-tetrahydroquinoxaline-2-carboxamide 4-oxide and
6,7-dimethyl-N-(4-methylcyclohexyl)-6,7-dihydro-5H-cyclopenta[b]pyrazine-2-carboxamide,
or salts thereof.

14. (Withdrawn and Previously Presented) A pharmaceutical composition comprising as active ingredient a therapeutically effective amount of the compound according to any one of claims 1 Reply to Office Action of March 29, 2007

or 2, in association with one or more pharmaceutically acceptable diluent, excipients and/or inert carrier.

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15. (Withdrawn) The pharmaceutical composition according to claim 14, for use in the treatment of Group I mGluR mediated disorders.

16.-18. (Cancelled)

19. (Withdrawn and Previously Presented) A method of treatment of Group I mGluR mediated disorders, comprising administering to a mammal, including man in need of such treatment, a therapeutically effective amount of the compound according to any one of claims 1 or 2.

20. (Withdrawn) The method according to claim 19, for use in treatment of neurological disorders

21. (Withdrawn) The method according to claim 19, for use in treatment of psychiatric disorders.

22. (Withdrawn) The method according to claim 19, for use in treatment of chronic and acute pain disorders.

23. (Withdrawn) The method according to claim 19, for use in treatment of gastrointestinal disorders.

24. (Withdrawn) A method for inhibiting activation of Group I mGluR receptors, comprising treating a cell containing said receptor with an effective amount of the compound according to claim 1 or 2.

25. (Withdrawn) Processes for the preparation of the compound according to claim 1 or 2,

wherein P, Q, X1, X2, R1, R2, R3, R4, m and n are, unless otherwise specified, defined as in formula I, comprising of: A

$$(R^{3})_{n} \xrightarrow{Q} N_{1} \xrightarrow{R^{4}} 0 \xrightarrow{R^{9}} HN^{-X^{2}} \xrightarrow{P} (R^{1})_{m} \xrightarrow{\qquad} (XIV)$$

$$(XIV) \xrightarrow{(R^{3})_{n}} Q \xrightarrow{N_{1}} N^{-X^{2}} \xrightarrow{P} (R^{1})_{m}$$

$$(R^{3})_{n} \xrightarrow{Q} N_{1} \xrightarrow{R^{4}} R^{2} \xrightarrow{P} (R^{1})_{m}$$

$$(II)$$

reacting a compound of formula VII, wherein Ry is H, with an activating agent followed by the treatment of the resulting acid halide, or otherwise to nucleophiles activated acid derivative, with an amine of formula XIV, to obtain the compound of formula I. alternatively,

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reacting an amine of formula XIV with the compound of formula VII, wherein  $R^{\gamma}$  is H, to obtain the compound of formula I. or

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$$(R^3)_n \qquad \qquad X^1 \qquad \qquad Y^1 \qquad \qquad$$

reacting a compound of formula VIa or the  $N_I$ -oxide thereof, wherein  $R^X$  is  $C_{1.6}$  alkyl, with the appropriate amine such as the compound of formula XIV, to obtain the compound of formula I,

or.

D

$$(R^3)_n \qquad Q \qquad Q \qquad + H_2N \qquad X^1 \qquad X^2 \qquad P \qquad (R^1)_m \qquad (R^3)_m \qquad (XVb)$$

$$(R^3)_n Q N_1 R^4 R^2 P (R^7)_m$$

direct condensation of intermediates of formula IV and XVb, to obtain the compound of formula I.

26. (Withdrawn) Compounds

5,6,7,8-tetrahydro-quinoxaline-2-carboxylic acid methyl ester and

5,6,7,8-tetrahydro-quinoxaline-2-carboxylic acid.

### 27. (Withdrawn) Compounds

3-methyl-5,6,7,8-tetrahydro-quinoxaline-2-carboxylic acid ethyl ester.

3-methyl-5,6,7,8-tetrahydro-quinoxaline-2-carboxylic acid,

2,3-diamino-N-(4-methyl-cyclohexyl)-propionamide.

4-(tert-butyl-diphenyl-silanyloxy)-cyclohexane-1,2-dione,

6,7-dimethyl-6,7-dihydro-5H-cyclopentapyrazine-2-carboxylic acid methyl ester,

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5,6,7,8-tetrahydro-quinoxaline-2-carboxylic acid methyl ester and

5,6,7,8-tetrahydro-quinoxaline-2-carboxylic acid.

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28. (Withdrawn) The compounds according to claims 26 and 27, for use as an intermediate in the preparation of the compound according to claim 1.

- 29. (Previously Presented) The compound according to claim 3, wherein X1 is oxygen.
- 30. (Previously Presented) The compound according to claim 4, wherein X1 is oxygen.
- 31. (Previously Presented) The compound according to claim 3, wherein X<sup>2</sup> is a bond.
- 32. (Previously Presented) The compound according to claim 4, wherein X<sup>2</sup> is a bond.
- 33. (Previously Presented) The compound according to claim 5, wherein X<sup>2</sup> is a bond.
- 34. (Previously Presented) The compound according to claim 3, wherein R<sup>2</sup> is hydrogen.
- 35. (Previously Presented) The compound according to claim 4, wherein R2 is hydrogen.
- 36. (Previously Presented) The compound according to claim 5, wherein R<sup>2</sup> is hydrogen.
- 37. (Previously Presented) The compound according to claim 6, wherein R<sup>2</sup> is hydrogen.
- 38. (Previously Presented) The compound according to claim 3, wherein R<sup>4</sup> is hydrogen or methyl.
- 39. (Previously Presented) The compound according to claim 4, wherein R<sup>4</sup> is hydrogen or methyl.
- 40. (Previously Presented) The compound according to claim 5, wherein R4 is hydrogen or methyl.

- 41. (Previously Presented) The compound according to claim 6, wherein R<sup>4</sup> is hydrogen or methyl.
- (Previously Presented) The compound according to claim 7, wherein R<sup>4</sup> is hydrogen or methyl.
- 43. (Previously Presented) The compound according to claim 3, wherein Q is a saturated or partially unsaturated ring containing 5, 6 or 7 atoms independently selected from C, O and N.
- 44. (Previously Presented) The compound according to claim 4, wherein Q is a saturated or partially unsaturated ring containing 5.6 or 7 atoms independently selected from C. O and N.
- 45. (Previously Presented) The compound according to claim 5, wherein Q is a saturated or partially unsaturated ring containing 5, 6 or 7 atoms independently selected from C, O and N.
- 46. (Previously Presented) The compound according to claim 6, wherein Q is a saturated or partially unsaturated ring containing 5.6 or 7 atoms independently selected from C. O and N.
- 47. (Previously Presented) The compound according to claim 7, wherein Q is a saturated or partially unsaturated ring containing 5. 6 or 7 atoms independently selected from C, O and N.
- 48. (Previously Presented) The compound according to claim 8, wherein Q is a saturated or partially unsaturated ring containing 5, 6 or 7 atoms independently selected from C, O and N.
- (Previously Presented) The compound according to claim 3, wherein R<sup>3</sup> is hydrogen, hydroxy, halogen, cyano, C<sub>1.3</sub>alkyl or C<sub>1.3</sub>alkoxyC<sub>0.3</sub>alkyl.

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- 50. (Previously Presented) The compound according to claim 4, wherein R<sup>3</sup> is hydrogen. hydroxy, halogen, cyano, C1-3alkyl or C1-3alkoxyC0-3alkyl.
- 51. (Previously Presented) The compound according to claim 5, wherein R<sup>3</sup> is hydrogen. hydroxy, halogen, cyano, Claalkyl or ClaalkoxyCoaalkyl.
- 52. (Previously Presented) The compound according to claim 6, wherein R<sup>3</sup> is hydrogen. hydroxy, halogen, cyano, Cialkyl or CialkoxyCoalkyl.
- 53. (Previously Presented) The compound according to claim 7, wherein R<sup>3</sup> is hydrogen. hydroxy, halogen, cyano, C1-3alkyl or C1-3alkoxyC0-3alkyl.
- (Previously Presented) The compound according to claim 8, wherein R<sup>3</sup> is hydrogen. hydroxy, halogen, cyano, C1-3alkyl or C1-3alkoxyC0-3alkyl.
- 55. (Previously Presented) The compound according to claim 9, wherein R<sup>3</sup> is hydrogen. hydroxy, halogen, cyano, C1-3alkyl or C1-3alkoxyC6-3alkyl.
- 56. (Previously Presented) The compound according to claim 3 having a trans-relationship between R1 and X2 on ring P, wherein P is cyclohexane, and R1 and X2 are attached to P at positions 4 and 1, respectively.
- 57. (Previously Presented) The compound according to claim 4 having a trans-relationship between R1 and X2 on ring P, wherein P is cyclohexane, and R1 and X2 are attached to P at positions 4 and 1, respectively.
- 58. (Previously Presented) The compound according to claim 5 having a trans-relationship between R1 and X2 on ring P, wherein P is cyclohexane, and R1 and X2 are attached to P at positions 4 and 1, respectively.

59. (Previously Presented) The compound according to claim 6 having a trans-relationship between R1 and X2 on ring P, wherein P is cyclohexane, and R1 and X2 are attached to P at

positions 4 and 1, respectively.

60. (Previously Presented) The compound according to claim 7 having a trans-relationship between R1 and X2 on ring P, wherein P is cyclohexane, and R1 and X2 are attached to P at

positions 4 and 1, respectively.

61. (Previously Presented) The compound according to claim 8 having a trans-relationship between R1 and X2 on ring P, wherein P is cyclohexane, and R1 and X2 are attached to P at

positions 4 and 1, respectively.

62. (Previously Presented) The compound according to claim 9 having a trans-relationship between R1 and X2 on ring P, wherein P is cyclohexane, and R1 and X2 are attached to P at

positions 4 and 1, respectively.

63. (Previously Presented) The compound according to claim 10 having a trans-relationship between R1 and X2 on ring P, wherein P is cyclohexane, and R1 and X2 are attached to P at

positions 4 and 1, respectively.

64. (Previously Presented) The compound according to Claim 1, wherein R4 is hydrogen, C1,

3alkyl, fluoromethyl, difluoromethyl, trifluoromethyl, methoxy, fluoromethoxy, difluoromethoxy, trifluoromethoxy, C1.3alkylamino, C1.3alkoxy, hydroxy,

65. (Previously Presented) The compound according to any one of Claims 1 or 2, wherein O is cyclohexyl, cyclohexenyl, cyclopentyl, cyclopentenyl, imidazolidinyl, imidazolinyl,

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morpholinyl, piperazinyl, piperidyl, piperidonyl, pyrazolidinyl, pyrazolinyl, pyrrolidinyl, pyrrolinyl, tetrahydropyranyl or thiomorpholinyl.

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